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Interappointment pain: mechanisms, diagnosis, and treatment

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Knowledge on the causes of and the mechanisms behind interappointment pain in endodontics is of utmost importance for the clinician to properly prevent or manage this undesirable condition. The causative factors of interappointment pain encompass mechanical, chemical, and/or microbial injury to the pulp or periradicular tissues, which are induced or exacerbated during root canal treatment. Microorganisms can participate in causation of interappointment pain in the following situations: apical extrusion of debris; incomplete instrumentation leading to changes in the endodontic microbiota or in environmental conditions; and secondary intraradicular infections. Interappointment pain is almost exclusively due to the development of acute inflammation at the periradicular tissues in response to an increase in the intensity of injury coming from the root canal system. When an interappointment emergency occurs, proper diagnosis and active treatment are required for the clinician to succeed in solving the problem. This review focuses on the mechanisms of interappointment pain, with special emphasis placed on the causative agents and the host response to injury that can precipitate pain. In addition, diagnostic measures and treatment approaches to manage interappointment pain are also discussed.

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The occurrence of postoperative pain of mild intensity is not a rare event even when endodontic treatment has followed acceptable standards. For the most part, mild pain after chemomechanical preparation can develop in about 10–30% of the cases (1–3), and in most instances the patient can bear the discomfort or can make use of common analgesics, which are usually effective in relieving symptoms. On the other hand, the development of interappointment pain of moderate to severe intensity, accompanied or not by swelling, has been demonstrated to be an unusual occurrence. However, these cases usually constitute a true emergency and very often require unscheduled visit for treatment.

Studies have reported frequencies of interappointment emergencies ranging from 1.4% to 16% (3–9). Certain factors have been suggested to significantly influence the development of interappointment pain, including age, gender, tooth type, pulpal status, presence of preoperative pain, allergies, and presence of sinus tract (3–5, 8, 9). In addition, fear of dental treatment, anxiety, apprehension, and possibly other psychological factors are known to influence the patient's pain perception and reaction thresholds (10). An association has been demonstrated between the presence of apprehension before endodontic treatment and postoperative pain (4, 11).

Knowledge on the causes of and the mechanisms behind interappointment pain is of utmost importance for the practitioner to properly prevent or manage this undesirable condition. When an interappointment emergency occurs, proper diagnosis and active treatment are required for the clinician to succeed in solving the problem. This review will focus on the mechanisms of interappointment pain, with special emphasis placed on the causative agents and the host response to injury that can precipitate pain. Moreover, diagnostic measures and treatment approaches to manage interappointment pain will also be discussed.

Causes of interappointment pain

The causative factors of interappointment pain comprise mechanical, chemical, and/or microbial injury to the pulp or periradicular tissues, which are induced or exacerbated during root canal treatment (5, 10). Regardless of the type of injury, the intensity of the inflammatory response is directly proportional to the intensity of tissue injury (12). Because vascular events associated with acute inflammation usually result in pain, it is conceivable to assume that the greater the intensity of the inflammatory reaction the greater the intensity of pain, even though other factors can influence the latter.

Mechanical and chemical injuries are often associated with iatrogenic factors, but microbial injury is arguably the major and the most common cause of interappointment pain (10, 13). This can be attested by the fact that the frequency of interappointment pain has been reported to be significantly higher in teeth with periradicular lesions as compared to teeth with vital pulps and normal periradicular tissues (8, 14). Microbial insult can also be coupled with iatrogenic factors to cause interappointment pain. Nevertheless, microbial involvement can play a role in pain causation even when root canal procedures have been performed judiciously and carefully.

Microbial causes

There are some special circumstances in which microorganisms can cause interappointment pain. Whatever the circumstances, interappointment pain will be most often a result of imbalance in host-bacteria relationship induced by intracanal procedures. Development of pain precipitated by infectious agents can be dependent on several factors, most of which are likely to be interconnected (15). These factors are as follows:

Presence of pathogenic bacteria

The progression of periradicular diseases from asymptomatic to symptomatic status has not been well documented. As a consequence, there is no evidence on the qualitative or quantitative shift in the endodontic microbiota that can accompany or cause exacerbations. This can make difficult the recognition of the bacterial species involved in the pathogenesis of symptomatic infections. However, circumstantial evidence has suggested that certain bacterial species can be associated with symptomatic periradicular lesions. These include *Porphyromonas endodontalis, Porphyromonas gingivalis, Prevotella* species, *Treponema denticola, Tannerella forsythia* (formerly *Bacteroides forsythus*), *Filifactor alocis, Dialister pneumosintes, Peptostreptococcus micros*, and *Finegoldia* (formerly *Peptostreptococcus*) *magna* (16–29). There is as yet a paucity of studies investigating the microbiota associated with interappointment pain. A recent study revealed that *F. nucleatum, Prevotella* species and *Porphyromonas* species were frequently isolated from flare-up cases (30). The possibility exists that the bacterial species associated with flare-ups are the same as those involved with primarily infected root canals associated with symptomatic periradicular lesions, although it remains to be confirmed. A puzzling factor related to this issue is that several studies have also found those bacterial species in asymptomatic cases (18–23, 25, 31), which raises the suspicion that their occurrence in such cases can predispose to flare-ups, provided that bacteria are somehow favored by conditions brought about during endodontic intervention. Furthermore, factors other than the presence of a given pathogenic species may certainly influence the development of periradicular pain and should also be taken into consideration (15).

Presence of virulent clonal types

Clonal types of a given pathogenic bacterial species can significantly diverge in their virulence ability (32–35). A disease ascribed to a given pathogenic species is in fact caused by specific virulent clonal types of that species. Thus, presence of virulent clones of candidate endodontic pathogens in the root canal may be a predisposing factor for interappointment pain, provided that conditions are created for them to exert pathogenicity.

Microbial synergism or additism

Most of the presumed endodontic pathogens only show virulence or are more virulent when in association with other species (36–40). This is because of synergic or additive microbial interactions, which can certainly influence virulence and play a role in symptom causation.

Number of microbial cells

The microbial load is well recognized as an important factor for a microorganism to cause disease. If the host

is faced with a higher number of microbial cells than it is used to dealing with, acute exacerbation of the periradicular lesion can occur. This can be accidentally precipitated by endodontic procedures (not necessarily iatrogenic ones) and causes for this will be discussed ahead in this paper.

Environmental cues

A virulent clone of a given pathogenic species does not always express its virulence factors throughout its lifetime. A great deal of evidence indicates that the environment exerts an important role in inducing the turning on or the turning off of microbial virulence genes (33, 41–45). Studies have demonstrated that environmental changes can influence the behavior of some putative oral (and endodontic) pathogens, including *P. gingivalis, F. nucleatum, P. intermedia,* and oral treponemes (46, 47). If the root canal environmental conditions are in someway altered by intracanal procedures and as a result become conducive to the expression of virulence genes, microbial virulence can be enhanced and interappointment pain can ensue.

Host resistance

The host resistance to infection is a factor of unquestionable importance dictating whether a disease will develop or not. It is well known that different individuals present different patterns of resistance to infections, and such differences can certainly become evident during individual's lifetime (15, 48). Hypothetically, individuals who had reduced ability to cope with infections may be more prone to develop clinical symptoms after endodontic procedures in infected root canals.

Herpesvirus infection

This is a factor that can be coupled with diminished host resistance. Herpesviruses have the ability to interfere with the host immune response, which may trigger overgrowth of pathogenic bacteria and/or diminish the host resistance to infection (49, 50). Moreover, herpesviruses may induce the release of proinflammatory cytokines by host defense cells (51). A recent study observed that active infections of periradicular lesions by human cytomegalovirus and/or Epstein–Barr virus were significantly associated with symptomatology (52). Thus, the possibility exists that active herpesvirus infections in periradicular lesions may initiate or contribute to flare-ups (53). The mechanisms behind herpesviruses involvement with symptomatic periradicular lesions remain elusive.

There are some situations during the endodontic treatment that can facilitate microorganisms to cause interappointment pain. These include: (a) apical extrusion of debris; (b) incomplete instrumentation leading to changes in the endodontic microbiota or in environmental conditions; and (c) secondary intraradicular infections (54).

(a) Apical extrusion of debris

Extrusion of infected debris to the periradicular tissues during chemomechanical preparation is allegedly one of the principal causes of postoperative pain (10, 54, 55). In asymptomatic periradicular lesions associated with infected teeth, there is a balance between microbial aggression from the infecting endodontic microbiota and the host defenses at the periradicular tissues. If during chemomechanical preparation microorganisms are extruded into the periradicular tissues, the host will face a situation in which it is now challenged by a larger number of irritants than it was before. Consequently, there will be a transient disruption in the balance between aggression and defense, in such a way that an acute inflammatory response is mounted to re-establish equilibrium.

The risks of interappointment pain during the treatment of infected cases can be even higher in the event of overinstrumentation. In those cases, exacerbations caused by iatrogenic overinstrumentation are likely to develop as a result of mechanical injury to the periradicular tissues, which is usually coupled with apical extrusion of a significant amount of debris containing microorganisms.

The incidence of postoperative pain in re-treatment cases with periradicular lesions has been demonstrated to be significantly high (5, 9, 56). During removal of the root filling material and further instrumentation, filling remnants and infected debris tend to be pushed ahead of the files and to be forced into the periradicular tissues, exacerbating inflammation and causing pain (9, 56). Solvents used during filling removal are also cytotoxic and may contribute to exacerbation of the periradicular inflammation (57).

Forcing microorganisms and their products into the periradicular tissues can generate an acute inflamma-

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tory response, whose intensity will depend on the number and/or virulence of the extruded microorganisms. Therefore, quantitative and qualitative factors will be decisive in causation of interappointment pain as a result of apical extrusion of debris. The quantitative factor comprises the number of microbial cells extruded (microbial load), while the qualitative factor encompasses the virulence of the extruded microorganisms. Admittedly, virtually all instrumentation techniques promote apical extrusion of debris (58–60). However, techniques significantly diverge as to the amount of extruded debris, with some techniques extruding less than others. Such differences in the amount of extruded debris may be crucial for the development of postoperative pain, as techniques that extrude more debris allegedly increase the risk for exacerbation to occur. Crown-down techniques, irrespective of whether hand or engine-driven instruments are used, usually extrude less debris and should be elected for the instrumentation of infected root canals. Therefore, the quantitative factor is more likely to be under control of the practitioner. On the other hand, the qualitative factor is more difficult to be controlled. If virulent clonal types of pathogenic bacterial species are present in the root canal system and are propelled to the periradicular tissues during instrumentation, even a small amount of infected debris will have the potential to cause or exacerbate periradicular inflammation.

(b) Incomplete instrumentation

The microbiota associated with primary endodontic infections is usually established as a mixed consortium, and alteration of part of this consortium will affect both the environment and the remaining species. Potent exogenous forces represented by chemomechanical preparation using antimicrobial irrigants and intracanal medication are needed to eradicate microbial communities from the root canal system. However, incomplete chemomechanical preparation can disrupt the balance within the microbial community by eliminating some inhibitory species and leaving behind other previously inhibited species, which can then overgrow (61). If overgrown strains are virulent and/or reach sufficient numbers, damage to the periradicular tissues can be intensified and then result in lesion exacerbation. Furthermore, environmental changes induced by incomplete instrumentation have the potential to induce virulence genes to be turned on. As a result of the increase in microbial virulence, a previously asymptomatic case may become symptomatic.

Another form of environmental change induced by endodontic intervention refers to the entrance of oxygen in the root canal. It has been suggested that this can alter the oxidation–reduction potential (Eh) in the root canal and, as a consequence, acute exacerbation can occur (62). This theory is based on the fact that the increase in Eh would induce microbial growth pattern to change from anaerobic to aerobic, with consequent overgrowth of facultative bacteria. Overgrowing facultative bacteria might precipitate acute periradicular inflammation. Proof of this theory is lacking and the proponent study is fraught with serious experimental flaws and questionable procedures – improper sampling procedures, initial office incubation before transfer to the laboratory, tooth left open for drainage, and incomplete instrumentation at the initial appointment (54). Because of this, this theory is considered only as speculative and there is no scientific evidence indicating it is valid.

(c) Secondary intraradicular infections

Secondary intraradicular infections are caused by microorganisms that were not present in the primary infection and have gained entry into the root canal system during treatment, between appointments, or even after the conclusion of the endodontic treatment (15). Introduction of new microorganisms into the root canal system can occur due to several ways, the most common being a breach of the aseptic chain during treatment (63). If the microorganisms that gain access to the root canal are successful in surviving into and colonizing such a new environment, a secondary infection will establish itself and may be one of the causes of postoperative pain, providing that the newly established microbial species are virulent and reach sufficient numbers to induce acute periradicular inflammation.

Non-microbial causes

Microorganisms are deemed to be essential for induction and perpetuation of periradicular diseases, inasmuch as they usually represent a persistent source of irritation. Non-microbial factors can also induce periradicular inflammation, which is however not

perpetuated since the irritation is usually transient (providing it is not overlapped with concomitant microbial aggression!). In spite of being transient, inflammation generated by non-microbial factors can obviously cause pain as well. Therefore, the ability to induce inflammation and pain is not only a 'privilege' of microorganisms.

Non-microbial causes are represented by chemical or physical factors that can inflict damage to the periradicular tissues and thereby can be responsible for the development of interappointment pain. The intensity of pain will depend on several aspects, including intensity of the injury, intensity of tissue damage, and intensity of the inflammatory response. All these three phenomena are interconnected, as one is directly dependent on the other.

When instruments, irrigants, medications, and filling materials have their use limited to the interior of the root canal system, the risks of pain due to physical or chemical injury is rather low. Indeed, non-microbial causes are usually associated with iatrogenic events. Examples of mechanical irritation causing periradicular inflammation include instrumentation (mainly overinstrumentation), and overextended filling materials. In cases of overinstrumentation, the larger the instrument, the larger the damage to the periradicular tissues. Consequently, the intensity of the inflammatory reaction will be high and so will the risk for postoperative pain to develop. Not to mention the fact that in infected cases, overinstrumentation will be coupled with extrusion of infected debris, as discussed above. Overextended filling materials mechanically compress the periradicular tissues and may induce pain.

Examples of chemical irritation include apical extrusion of irrigants or intracanal medications. Most irrigants and medications are cytotoxic to the host tissues, and because of this their use should be restricted to the root canal. In spite of being cytotoxic, clinical trials have shown that substances used for irrigation or intracanal medication may have no influence on the occurrence of postoperative symptoms (5, 64). However, severe reactions have been reported after extrusion of some commonly used substances to the periradicular tissues (65–69). Overextended filling materials also represent chemical irritation to the periradicular tissues, as virtually all endodontic sealers exhibit different degrees of cytotoxicity, at least before setting (70). Although there does not seem to be a clear correlation between the occurrence of sealer extrusion and the intensity of postobturation pain (71), one should assume that the larger the amount of overextended material, the greater the intensity of damage to the periradicular tissues. Therefore, large overfillings admittedly increase the risks of pain.

Inflammatory events leading to interappointment pain

Interappointment pain is almost exclusively due to the development of acute inflammation at the periradicular tissues in response to an increase in the intensity of injury coming from the root canal system. The inflammatory response to tissue injury can be regarded as a double-edged sword. On the one hand, it provides protection against infection and/or prepares the injured area for repair of the tissue architecture. On the other hand, inflammatory reaction can result in undesirable effects such as pain and intensified tissue damage.

As previously mentioned, microorganisms are the major causative agents of periradicular inflammation. Whatever the mechanisms by which microorganisms are involved, interappointment pain is a result of acute periradicular inflammation in response to a sudden increase in the amount of microbial irritants. Under such circumstances, the host is challenged by a higher number of microbial cells and/or products than it was used to coping with, and as a consequence the balance between aggression and defense is disrupted. Then the host mounts an acute inflammatory reaction at the periradicular tissues in an attempt to re-establish the equilibrium. Chemical mediators released after tissue injury can directly lower the excitability threshold of the sensory nerve fibers, can induce pain due to direct effect on the nerve fibers, or can cause pain indirectly by inducing increase of the vascular permeability, which produces edema and swelling (12, 54, 72).

In the majority of circumstances in which interappointment pain is caused by microorganisms, an infection is established in the root canal system and the periradicular tissues are usually chronically inflamed. Bacteria that suddenly gain access to the periradicular tissues are faced with two immediate lines of defense, represented by the complement system and by phagocytes (neutrophils and macrophages) present in the chronically inflamed tissue. Bacteria may be recognized directly and engulfed by neutrophils and macrophages with receptors for common bacterial components (73).

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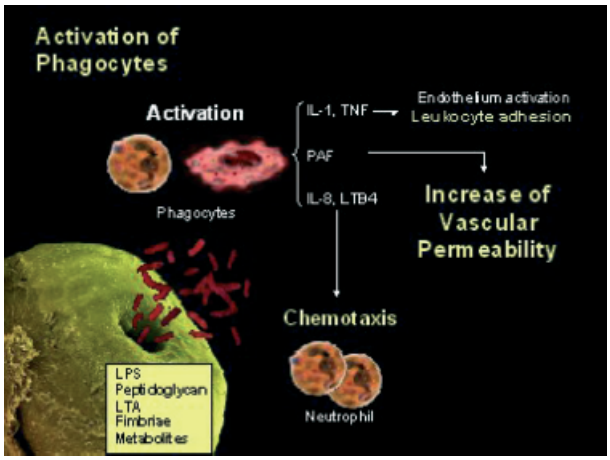

Fig. 1. Microbial cells and products egressing from the root canal to the periradicular tissues induce activation of phagocytes, with consequent release of chemical mediators involved in inflammation (for more details, see text).

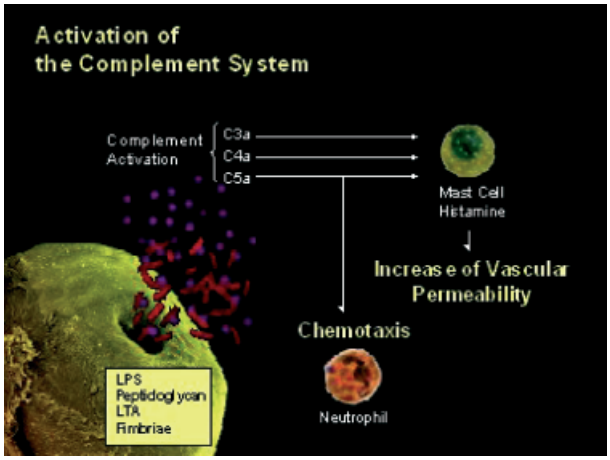

Fig. 2. Microbial cells and products egressing from the root canal to the periradicular tissues induce activation of the complement system, with consequent release of chemical mediators involved in inflammation (for more details, see text).

The activation of complement by the classic, alternative, and/or lectin pathways and the engulfment of bacteria by phagocytes can occur in the early hours of host-pathogen interaction in an already inflamed tissue. The encounter of the bacteria with these host defense mechanisms triggers the production and release of chemical mediators of inflammation, which will induce vascular changes in the microcirculation and recruit new phagocytic cells to the site (Figs 1 and 2).

The bacterial mass contacting the periradicular tissues may contain large quantities of virulence factors that diffuse through tissues and activate host defenses. These factors include cellular constituents (such as lipopolysaccharide, peptidoglycan, lipoteichoic acid, fimbriae), metabolic end products (such as butyrate, propionate and sulfur compounds), and peptides containing *N*-formyl-methionine-leucyl-phenylalanine. Bacterial cell constituents can activate macrophages as well as the complement system via the alternative pathway (73). Bacteria that express mannose on their surface can lead to complement activation by the lectin pathway (74). Since antibodies specific to intracanal microorganisms are already being produced in a periradicular lesion (75, 76), the complement system can also be activated by the classic pathway. Metabolic end products are toxic to tissues and can induce release of pro-inflammatory cytokines (77, 78). *N*-formyl-methionine-leucyl-phenylalanine peptides are chemoattractants to neutrophils (79). Only bacterial proteins and few mammalian proteins (those synthesized within mitochondria) are initiated by *N*-formyl-methionine-leucyl-phenylalanine, and receptors found on neutrophils allow them to detect and to respond to bacterial proteins.

Phagocytic cells are usually strategically placed at all sites where microorganisms may gain entry into the host. Phagocytes usually accumulate in the tissue area adjacent to the apical foramen of infected root canals (80), in an attempt to prevent bacterial invasion of the periradicular tissues (obviously in a teleological sense!). In response to bacterial challenge, phagocytes can release a variety of mediators, such as cytokines (IL-1, IL-6, IL-8, IL-12, TNF-α), prostaglandins, oxygen-derived radicals, leukotrienes (particularly LTB4), and platelet-activating factor (PAF) (81–85) (Fig. 1). In addition to these products of phagocytes, the activation of the complement system by any of the three pathways generates mediators such as C5a and C3a, both of which can activate mast cells, causing them to release histamine (86, 87) (Fig. 2). Histamine causes dilation of arterioles and increases permeability of venules (88). C5a is a powerful chemotactic agent for neutrophils and monocytes. The combined local effects of these mediators result in exacerbation of the inflammatory response, which usually starts immediately after increase in bacterial aggression and may take some hours before signs and symptoms become evident.

Increased vascular permeability is the hallmark of acute inflammation. Together with the increased hydrostatic pressure secondary to vasodilation, the increase in the vascular permeability leads to a marked outflow of fluid and its accumulation in the extravascular

space. The inflammatory exudate leaving the vessels and accumulating in tissues will elevate the tissue hydrostatic pressure, which results in swelling and pain. Endothelium usually becomes leaky in inflammation due to: (a) formation of gaps between endothelial cells in venules, which is elicited by mediators such as histamine, bradykinin, leukotrienes, PAF, and substance P; (b) direct endothelial cell injury induced by direct damage to the endothelium by the injurious agent; (c) or endothelium injury mediated by leukocytes which adhere to endothelium early in inflammation and, if activated in the process, they can release oxygen radicals and lysosomal enzymes, causing endothelial injury (89).

Although some mediators can cause pain through direct stimulation of sensory nerve fibers, the exuded fluid produces pressure on sensory nerve endings and is arguably the major factor responsible for pain associated with acute inflammation (12, 54). Exudation induces an increase in tissue hydrostatic pressure, with resultant compression of nerve endings and pain generation, provided that pressure is sufficiently high to reach the excitability threshold of periodontal nerve fibers. The high tissue pressure also can distend soft tissues and cause swelling. Taking into account the pivotal role played by the increased tissue hydrostatic pressure in causation of pain of endodontic origin, the axiom for the emergency treatment of cases with severe pain is drainage of the exudate, thus diminishing the tissue pressure.

In addition to inducing vascular changes in the periradicular tissues, the bacterial challenge will also precipitate events leading to the recruitment of more phagocytic cells to the area. This usually increases the host's ability to cope with infection, but excessive recruitment of neutrophils coupled with intense damage to the periradicular tissues can result in abscess formation.

IL-1 and TNF secreted by macrophages in response to bacteria stimulate endothelial cells to sequentially express different molecules that mediate the preferential attachment of different types of leukocytes (89). Bacterial products, such as LPS, may also act directly on endothelial cells to promote the same kinds of changes induced by TNF (90). Slowing of the blood flow as a result of the increase in vascular permeability and activation of endothelial cells by mediators such as IL-1, TNF and LPS, generates conditions that are propitious for leukocytes to marginate along the

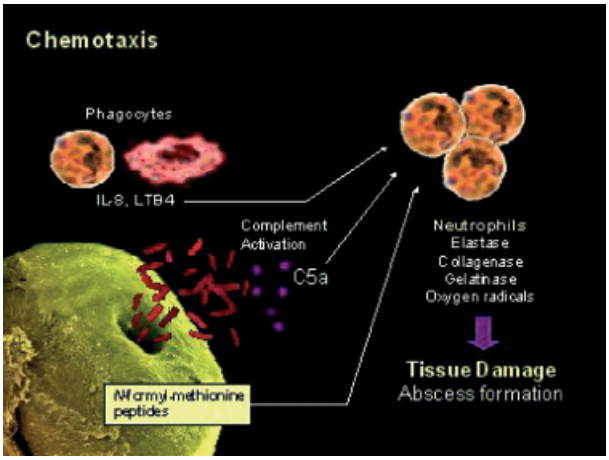

Fig. 3. Microbial products and host-derived chemical mediators damage will recruit neutrophils to the inflamed area. This increases host's ability to deal with the infection but at the same time it can have destructive effects due to the release of lisosomal enzymes and oxygen radicals by neutrophils, leading to pus formation (for more details, see text).

endothelial lining, roll on it and then to adhere to endothelial cells. As the leukocyte is rolling on the surface of and then adheres to the endothelium, it may become activated by chemokines that are displayed on endothelial cells. In response to chemokines, leukocytes rearrange their cytoskeletons, undergo morphological transition from a spherical to a flattened shape and become more motile (91). Afterward, they start transmigration across the endothelium and after extravasation they emigrate in tissues toward the site of injury by means of chemotaxis. Chemotactic substances include bacterial factors (such as *N*-formyl-methionine-leucyl-phenylalanine peptides) and host-derived factors (particularly chemokines, C5a, and LTB4), which act on leukocytes to stimulate migration and activate microbicidal functions (89, 92) (Fig. 3). Once in the tissue, leukocytes migrate toward a gradient of chemoattractant through the connective tissues by using their surface integrins to crawl along the fibrin or fibronectin scaffold that is formed from extravasated plasma proteins.

Polymorphonuclear neutrophils are the first leukocytes to migrate to the injured area. Neutrophils exposed to IL-8 and TNF-α are activated to mediate a respiratory burst that generates oxygen radicals, and to release their stored granule contents, thus contributing to the elimination of bacteria from the site. However, when neutrophils and macrophages are strongly activated or challenged, tissue damage can

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also ensue, as oxygen radicals and lysosomal enzymes are not able to distinguish between host tissues and bacteria. The extreme form of tissue injury by neutrophils responding to bacteria is abscess formation (Fig. 3).

Of the several proteolytic enzymes contained in neutrophil granules, three enzymes (elastase, collagenase, and gelatinase) seem to have a great potential to be involved with host tissue destruction by degrading components of extracellular matrix of the connective tissue (12). The metabolic and membrane perturbations that occur in neutrophils during chemotaxis, activation, and phagocytosis result in the release of products not only within the phagolysosome, but also potentially in the extracellular environment. The ways by which lisosomal enzymes can be released from neutrophils are the following (89):

(a) death of the cell, resulting in leakage of enzymes into the surrounding tissues;
(b) lysis of the cell induced by bacterial products;
(c) fusion of the lysosome with phagocytic vacuoles before the vacuoles have been completely formed, resulting in leakage of the enzymes; and
(d) discharge of lysosomal enzymes into the medium when the cell is brought into contact with targets difficult to be ingested (large colonies, bacteria adhered to flat surfaces, etc).

In brief, a sudden egress of a large mass of bacteria into the periradicular tissues represent a great amount of bacterial cells and products that can cause a massive emigration of neutrophils, which can subsequently die or be unable to phagocytose large bacterial masses or encapsulated bacteria. Consequent leakage of lisosomal enzymes and oxygen radicals into the surrounding tissues will lead to pus formation and an abscess is established.

Not only can microorganisms cause periradicular inflammation, but also any other factor that inflicts damage on the periradicular connective tissues. Physical or chemical injury to the periradicular tissues during chemomechanical preparation can cause degranulation of mast cells, with consequent release of histamine into the periradicular tissues (Fig. 4). Physical or chemical factors can also cause damage to the blood vessels at the periradicular tissues, with consequent activation of several cascades triggered by the Hageman factor (Fig. 4). Vascular damage allows this factor to contact negatively charged surfaces, such as collagen and basement membrane, which results in its activation.

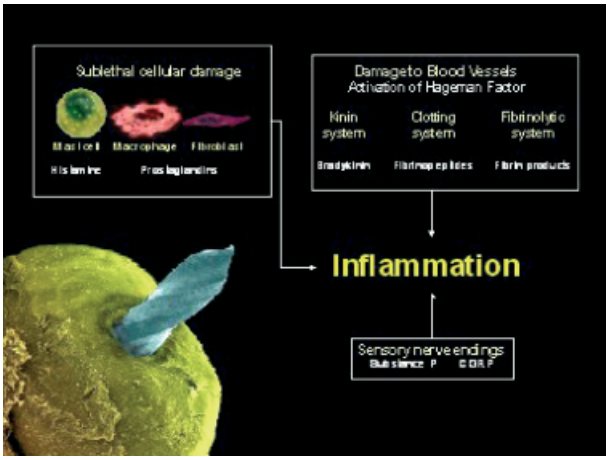

Fig. 4. Damage to the periradicular tissues caused by mechanical (e.g., overinstrumentation) or chemical (e.g., apical extrusion of irrigants) injury can precipitate a myriad of events, which will lead to inflammation (for more details, see text).

Activated Hageman factor initiates systems involved in inflammation: the kinin system, the clotting system and the fibrinolytic system. Bradykinin formed after activation of the kinin system is a potent agent that increases vascular permeability. The activation of the clotting system results in thrombin activation, which in turn cleaves circulating soluble fibrinogen to generate a fibrin clot. During conversion, fibrinopeptides are formed which induce increase in the vascular permeability and chemotactic activity for leukocytes. Activation of fibrinolytic system generates plasmin, which degrades fibrin to form fibrin degradation products. These fibrin products may also induce increased vascular permeability. Therefore, activation of these three systems can contribute to the induction of acute inflammatory reaction and its consequences, such as swelling and pain. Sublethal cellular damage induced by chemical and physical factors can result in the production and release of arachidonic acid metabolites, such as prostaglandins and leukotrienes, which can play a role in the increase of vascular permeability and chemotaxis to leukocytes, respectively (88, 93) (Fig. 4). Damage to and/or stimulation of sensory nerve fibers can also induce release of neuropeptides, such as substance P and calcitonin gene-related peptide, which can cause vasodilation and increase of the vascular permeability (94, 95) (Fig. 4).

A study found a highly significant association between the presence of allergies to various substances (sulfa medication, pollen, dust, and foodstuffs) and the

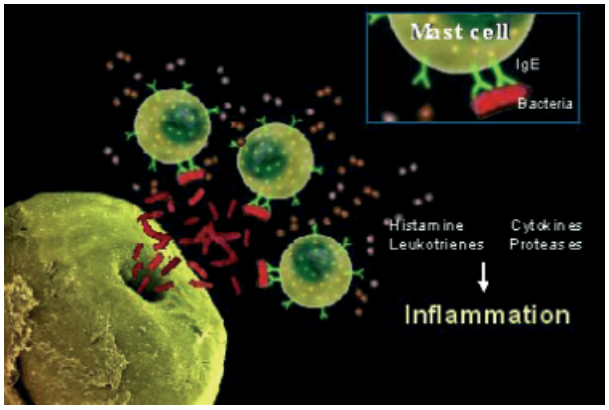

Fig. 5. Hypersensitivity reaction. Reintroduction of an antigen in a sensitized host may induce mast cells to release chemical mediators of inflammation (for more details, see text).

frequency of interappointment pain (5). It was suggested that this association could have been due to immediate hypersensitivity reaction occurring in the periradicular tissues in response to the egress of antigens from the root canal. Immediate hypersensitivity is a rapid, IgE antibody and mast cell-mediated vascular reaction, often accompanied by inflammation, which occurs in some individuals upon encounter with certain antigens to which they have been exposed previously (90). Individuals with a strong propensity to develop immediate hypersensitivity reactions are said to be atopic. Severity of the reaction may vary in different individuals. Basically, the sequence of events consists of the production of IgE in response to a given antigen, binding of IgE to receptors on mast cells, cross-linking of the bound IgE by reintroduced antigen, and release of mast cell mediators, some of which can cause a rapid increase in vascular permeability (87) (Fig. 5). Reaction may develop within minutes of re-introduction of the antigen.

In individuals who are prone to allergies, encounter with some protein antigens or chemicals that bind to proteins elicits activation of T_H2 cells and IgE production. Atopic individuals produce large amounts of IgE in response to antigens that do not elicit IgE responses in most individuals. IgE antibody produced in response to an antigen binds to high-affinity Fc receptors expressed on mast cells. In atopic individuals, mast cells are coated with IgE specific for the antigen to which the individual is allergic. In normal individuals, by contrast, mast cells may carry IgE molecules of many specificities, not enough to cause immediate hypersensitivity responses. Mast cell activation occurs after binding of the antigen to two or more IgE molecules on the cell surface. The most important mediators released from mast cells are histamine, prostaglandins, leukotrienes, cytokines, and proteases (90) (Fig. 5). Histamine and leukotrienes cause increase in vascular permeability while prostaglandins cause vasodilation. Proteases may also cause damage to the local tissues. Cytokines induce local inflammation. Therefore, mast cell mediators are responsible for vascular reactions typical of acute inflammation. Although the components of immediate hypersensitivity reaction, e.g., IgE, mast cells, and mast cell-derived mediators, have been disclosed in periradicular lesions (96–102), evidence is lacking as to whether this reaction actually occurs in the periradicular tissues and are responsible for interappointment pain. Hypersensitivity reaction develops within minutes to an hour after exposure to antigens to which the host is sensitized, and interappointment pain takes some hours after intervention to occur. Also to be elucidated is whether and which antigens egressing from the root canal system to the periradicular tissues can evoke hypersensitivity reactions in atopic patients. Further, such association between allergy and interappointment pain has not been confirmed by others (8). While these questions are not properly addressed, there does not appear to be advantageous to prescribe antihistamine drugs to prevent interappointment emergencies in allergic patients.

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Treatment of interappointment pain

As previously stated, contemporary endodontic treatment is usually pain-free during the entire operative procedure. However, in a prospective clinical study on post-treatment pain, it was found that 21% of the patients reported slight pain, 15% had moderate pain and 7% experienced severe pain (2). Although some patients may experience some level of pain after root canal treatment, very few experience the 'true' flare-up, which requires an unscheduled office visit and/or the prescribing of analgesics, systemic steroids and antibiotics (3–9).

Hargreaves and Seltzer (103) described an integrated approach for the management and control of odontogenic pain. This has been termed the '3D' approach for pain control: *D*iagnosis, *D*efinitive treatment, and *D*rugs.

Diagnosis

The initial phase of treating the endodontic pain patient is of course diagnosis (104, 105). For the patient that has recently had an endodontic procedure the diagnosis is often quite simple. However, there are several conditions that have been shown to mimic endodontic or odontogenic pain (105–109). Additionally, the current episode of pain may be coming from another tooth, an unrelated sinus or TMJ-related condition or post-injection sequelae (110, 111). Perhaps the original endodontic diagnosis was incorrect. Obtaining a thorough understanding of the patient's chief complaint should be the first step in proper management. Gathering information, such as on when the post-treatment symptoms began, are they intermittent or continuous, are they mild, moderate or severe, is there an associated swelling and does anything exacerbate or alleviate the symptoms will assist the clinician in his assessment of the situation. A review of the patient medical and dental history is in order. A thorough clinical examination should then be performed. The following conditions should be properly noted: areas of swelling, discoloration, ulcerations, exudation, defective and/or lost restorations, cracked or fractured teeth and apparent changes in occlusal relationships. Clinical testing should include percussion (both in axial and right-angle direction), apical palpation, bite-stick challenge, thermal stimulation (cold and hot if indicated) and periodontal probing. The clinician must decide if taking additional radiographs are indicated. Often times, taking additional, properly angulated radiographs may further elucidate the etiology of the current condition. However, interpreting the presence of bone lesions is often difficult (112–114). These combined clinical and radiographic tests may reveal that the symptoms are non-odontogenic, are related to another tooth, or are in fact, related to the recently treated tooth.

Definitive treatment

When the endodontic pain patient presents for 'emergency' reevaluation and subsequent treatment, it should be understood that he/she may be in acute physical and emotional distress (14). It is incumbent upon the clinician to reassure the patient, explain that such post-treatment sequelae occur and then effectively treat the patient in such a way as to break the pain cycle.

Fig. 6. Pus drainage through the root canal system. Drainage allows for the exudative components to be released from the periradicular tissues thus reducing localized tissue pressure (courtesy of Dr Gilberto Debelian).

Once the diagnosis has been confirmed that in fact it is the recently treated tooth that is responsible for the post-treatment symptoms, definitive effective treatment must be rendered.

(a) Re-instrumentation

Definitive treatment may involve re-entering the symptomatic tooth. The involved tooth or area should be properly anesthetized prior to any treatment. The access cavity should then be opened and additional anatomy looked for that might have been missed on the initial visit. Enhanced magnification and illumination are beneficial in this regard (106, 115–117). Working lengths should be reconfirmed, patency to the apical foramen obtained and a thorough debridement with copious irrigation performed. Remaining tissue, microorganisms and toxic products or their extrusion are arguably the major elements responsible for the post-treatment symptoms (54). Occasionally, a suppurative exudation may be established through the root canal system (Fig. 6). Drainage will allow for the exudative components to be released from the periradicular tissues thus reducing localized tissue pressure (118). However, controversy exists as to whether leaving teeth open to drain or closing them to prevent additional contamination from the oral cavity provides the most

effective method of pain relief (8, 118, 119). It has been pointed out that leaving a tooth open is the most direct way to allow for re-infection via the oral microbiota (54).

Weine (120) advocated 'violating' and enlarging the apical constriction to at least a size #25 endodontic file to allow for drainage through the tooth. Nonetheless, Harrington and Natkin (121) stated that trephination through the apical foramen does not ensure drainage of periradicular exudation.

(b) Cortical trephination

Cortical trephination is defined as the surgical perforation of the alveolar bone in an attempt to release accumulated periradicular tissue exudate (122, 123). Various studies have evaluated the effectiveness of cortical trephination to prevent and/or relieve post-treatment pain (124–129). Chestner et al. (124) reported pain relief in patients with severe and recalcitrant periradicular pain when cortical trephination was performed. Additionally, in the asymptomatic patient, cortical trephination has been shown to decrease by 16–25% post-operative pain incidence when performed prophylactically (126, 127). Moos et al. (125) compared the difference in post-operative pain relief in patients with acute periradicular pain of pulpal origin when treated by either pulpectomy alone or pulpectomy with cortical trephination. There were no significant differences between the groups. Nist et al. (129) performed a randomized blinded study to evaluate post-operative pain and swelling after performing trephination in symptomatic teeth with periradicular radiolucent lesions. They also found no significant reduction in pain or swelling in the trephination group. As such, there appears to be no significant benefit from cortical trephination procedures (123).

(c) Incision and drainage (I&D)

In cases of acute exacerbation of a chronic periradicular lesion or a *de novo* post-treatment endodontic abscess, establishing drainage through the oral mucosa provides for effective emergency management. The rationale for an I&D procedure is to facilitate the evacuation of pus, microorganisms and toxic products from the periradicular tissues. Moreover, it allows for the decompression of the associated increased periradicular tissue pressure

Fig. 7. Localized intra-oral swelling. These cases are usually treated by means of I&D and root canal intervention. Antibiotics are rarely needed in cases like this.

Fig. 8. Diffuse extra-oral swelling. In addition to I&D procedures, antibiotics are usually prescribed in cases like this.

and provides significant pain relief. In teeth where the endodontic treatment has not yet been completed, it may be advisable to re-enter the root canal system to further eliminate the original etiologic factors via debridement, irrigation and the placement of an antimicrobial dressing. If the abscess occurs after the obturation of the root canal system, incision of the fluctuant tissue is perhaps the only reasonable emergency treatment, provided the root canal filling is adequate. In cases of poorly filled canals and in addition to incision, the filling material should be removed in order to allow for additional pus drainage through the root canal space. Antibiotics are usually not indicated in

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cases of a localized abscess (130) (Fig. 7), but they can be used to supplement clinical procedures in cases where there is poor drainage and if the patient has a concomitant trismus, cellulitis, fever or lymphadenopathy (Fig. 8). In addition, aggressive incision for drainage has been advocated for any infection with a cellulitis, regardless of whether it is fluctuant or indurated (131). However, there is not full agreement on this issue. Many clinicians have experienced significant healing of facial cellulitis infections after thorough debridement and disinfection of the root canal system supported by the systemic administration of antibiotics (123).

(d) Intracanal medicaments

Clinical studies have demonstrated that post-treatment pain is neither prevented nor relieved by medicaments such as formocresol, camphorated paramonochlorophenol, eugenol, iodine potassium iodide, Ledermix, or calcium hydroxide (5, 7, 132). However, the use of intracanal steroids (133), non-steriodal antiinflammatory drugs (NSAIDs) (134) or a corticosteroid–antibiotic compound (135) has been shown to reduce post-treatment pain. Rogers et al. (134) demonstrated that both dexamethasone and ketorolac when placed in the root canals of vital teeth after pulpectomy procedures showed statistically significant pain relief at the 12-h time period as compared to the placebo group. No adverse reactions were found following their placement within the root canal system. Negm (135) placed a corticosteroid–antibiotic compound (containing nystatin, neomycin, gramicidin and triamcinolone acetonide in an aqueous cream base), or a placebo (aqueous cream), in the root canals of patients who had returned with post-operative pain following endodontic treatment. It was found that the corticosteroid-antibiotic compound was significantly more effective than the placebo in providing pain relief at all time periods up to 24 h. As such, it appears that only steroids and NSAIDs when placed within the root canals system after debridement procedures can reduce or prevent post-treatment pain (14).

(e) Occlusal reduction

There appears to be minimal agreement in the dental literature as to benefit of reducing the occlusion to prevent post-endodontic pain. Creech et al. (136) and Jostes et al. (137) have shown that routine occlusal reduction for the prevention of post-operative pain was ineffective. Nevertheless, Rosenberg et al. (138) demonstrated that in teeth with pain upon biting, occlusal reduction was effective in reducing post-operative pain. Sensitivity to biting and chewing is perhaps due to increased levels of inflammatory mediators that stimulate periradicular nociceptors. Occlusal reduction may therefore alleviate the continued mechanical stimulation of the sensitized nociceptors (123).

Drugs

(a) Antibiotics

In a review on the use of systemic antibiotics for the control of post-treatment endodontic pain, Fouad (139) concluded that their use is without justification. However, it appears that antibiotics are frequently prescribed to the endodontic pain patient (140, 141). Current advances in our understanding of the biology of the infectious and inflammatory process, along with the known risks associated with antibiotics, such as the emergence of multiresistant bacterial strains, strongly indicate that the clinician should seriously re-evaluate their prescribing habits (139).

(b) Non-narcotic analgesics

Non-narcotic analgesics, NSAIDs and acetominophen have effectively been used to treat the endodontic pain patient. These drugs produce analgesia by actions in both the peripherally inflamed tissues as well as in certain regions of the brain and spinal cord (103, 105, 142). The NSAIDs have been shown to be very effective for managing pulpal and periradicular pain (103, 143). In patients with known sensitivity to NSAIDs or aspirin, and who have gastrointestinal ulcerations or hypertension due to renal effects of NSAID's, acetominophen should be considered for post-treatment pain (105, 144). The results of several double blind placebo-controlled trials in endodontic pain patients indicated that 400 mg ibuprofen, 50 mg ketoprofen, 100 mg flurbiprofen and 30–60 mg ketorolac all produce significant analgesia as compared to placebo (11, 103, 105, 145). Ibuprofen is generally considered the prototype of NSAIDs and has a well-documented efficacy and safety profile (143, 146, 147). Although there are few endodontic studies that

compared one NSAID with another, 400 mg ibuprofen was shown to be similar to 50 mg of ketoprofen (11).

Pretreatment with NSAIDs for irreversible pulpitis should have the effect of reducing pulpal and periradicular levels of the inflammatory mediator PGE2. The parenteral NSAID ketorolac tromethamine, when injected intraorally or intramuscularly, produced significant analgesia in patients with severe odontogenic pain prior to treatment (105, 145, 148). Administration of NSAIDs alone is usually sufficient for most endodontic pain patients who can tolerate this drug class. Ibuprofen 600 mg taken every 6 h is optimal for managing pulpal and periradicular pain of inflammatory origin (103). The combination of a NSAID and acetominophen taken together show additive analgesia for treating dental pain (103, 105, 149–151). However, for those patients that cannot tolerate this drug class one should consider 1000 mg acetominophen (103, 104). For pain that is not controlled by NSAIDs and acetominophen, narcotic analgesics are required. These may be given in combination with NSAIDs for additive effects (151, 152).

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